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DECLARATION

I, Jane Roberta Mann, B.A., a Translator, of Frank B. Dehn & Co., 59 St. Aldates, Oxford OX1 1ST, do solemnly and sincerely declare that I have a competent knowledge of the English and German languages and that the following is a true and accurate translation of DE 101 09 021.8 of 24th February 2001, Case 5/1315 of Boehringer Ingelheim Pharma KG.

I further declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true.

I acknowledge that wilful false statements and the like are punishable by fine or imprisonment, or both [18 U.S.C. 1001] and may jeopardize the validity of the application or any patent issuing thereon.

A handwritten signature in black ink, appearing to read "Jane Mann". It is written over a horizontal line.

Signed this 27th day of May, 2003



FEDERAL REPUBLIC OF GERMANY

Certificate of priority relating to the filing of a patent application

File number: 101 09 021.8

Date of application: 24th February 2001

Applicant/Proprietor: Boehringer Ingelheim Pharma KG,
Ingelheim/DE

Title: Xanthine derivatives, the preparation thereof and their use as
pharmaceutical compositions

IPC: C 07 D, A 61 K

**The attached papers are a true and exact copy of the original documents of this
application.**

Munich, 25th January 2002
German Patent and Trademark Office
The President
per pro

(signed)

Wehner

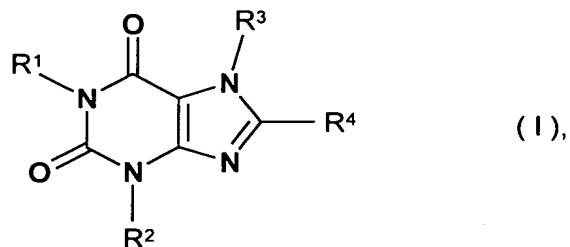
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Boehringer Ingelheim Pharma KG
D-55216 Ingelheim/Rhein

Case 5/1315-Ro

Xanthine derivatives, the preparation thereof and their use as pharmaceutical compositions

The present invention relates to substituted xanthines of general formula



the tautomers, the stereoisomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV), the preparation thereof, the use thereof for preventing or treating illnesses or conditions connected with an increased DPP-IV activity or capable of being prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, the pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof and processes for the preparation thereof.

In the above formula I

R¹ denotes a hydrogen atom,

a straight-chained or branched C₁₋₆-alkyl group,

a straight-chained or branched C₁₋₆-alkyl group substituted by a group R_a, wherein

R_a denotes a C₃₋₇-cycloalkyl, phenyl, cyano, carboxy, C₁₋₃-alkoxy-carbonyl, aminocarbonyl, C₁₋₃-alkylamino-carbonyl, di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

a straight-chained or branched C₂₋₆-alkyl group substituted by a group R_b, wherein

R_b is isolated by at least two carbon atoms from the cyclic nitrogen atom and

R_b denotes a hydroxy, C₁₋₃-alkoxy, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl or 4-ethylpiperazin-1-yl group,

a C₃₋₆-cycloalkyl group,

or a C₃₋₄-alkenyl or C₃₋₄-alkynyl group wherein the multiple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R² denotes a hydrogen atom,

a straight-chained or branched C₁₋₆-alkyl group,

a straight-chained or branched C₁₋₆-alkyl group substituted by a group R_a, wherein

R_a denotes a C₃₋₇-cycloalkyl, phenyl, cyano, carboxy, C₁₋₃-alkoxy-carbonyl, aminocarbonyl, C₁₋₃-alkylamino-carbonyl or di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

a straight-chained or branched C₂₋₆-alkyl group substituted by an R_b group, wherein

R_b is isolated from the cyclic nitrogen atom by at least two carbon atoms and

R_b denotes a hydroxy, C₁₋₃-alkoxy, amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl or 4-ethylpiperazin-1-yl group,

a C₃₋₆-cycloalkyl group,

or a C₃₋₄-alkenyl or C₃₋₄-alkynyl group, wherein the multiple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R³ denotes a straight-chained or branched C₁₋₆-alkyl group,

a straight-chained or branched C₁₋₆-alkyl group substituted by a group R_c wherein

R_c denotes a C₃₋₇-cycloalkyl group optionally substituted by a C₁₋₃-alkyl group,

a C₅₋₇-cycloalkenyl group optionally substituted by a C₁₋₃-alkyl group,

a phenyl group optionally substituted as defined hereinafter or

a furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group optionally substituted by one or two methyl or ethyl groups,

a straight-chain or branched C₃₋₈-alkenyl group, wherein the double bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

a straight-chain or branched C₃₋₆-alkenyl group substituted by a chlorine or bromine atom or a phenyl or trifluoromethyl group, wherein the double bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

or a straight-chain or branched C₃₋₆-alkynyl group wherein the triple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R⁴ denotes an azetidin-1-yl or pyrrolidin-1-yl group which is substituted in the 3 position by a R_eNR_d group and may additionally be substituted by a C₁₋₃-alkyl group, wherein

R_e denotes a hydrogen atom or a C₁₋₃-alkyl group and

R_d denotes a hydrogen atom, a C₁₋₃-alkyl group, an R_fC₁₋₃-alkyl group or an R_g-C₂₋₃-alkyl group, wherein

R_f denotes a carboxy, C₁₋₃-alkyloxy-carbonyl, aminocarbonyl, C₁₋₃-alkyl-amino-carbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, 2-cyanopyrrolidin-1-yl-carbonyl, 2-carboxypyrrolidin-1-yl-carbonyl, 2-methoxycarbonylpvrrolidin-1-yl-carbonyl, 2-ethoxycarbonylpvrrolidin-1-yl-carbonyl, 2-aminocarbonylpvrrolidin-1-yl-carbonyl, 4-cyanothiazolidin-3-yl-carbonyl, 4-carboxythiazolidin-3-yl-carbonyl, 4-methoxycarbonylthiazolidin-3-yl-carbonyl, 4-ethoxy-carbonylthiazolidin-3-yl-carbonyl, 4-aminocarbonylthiazolidin-3-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-methyl-piperazin-1-yl-carbonyl or 4-ethyl-piperazin-1-yl-carbonyl group and

R_g , which is separated by two carbon atoms from the nitrogen atom of the R_eNR_d group, denotes a hydroxy, methoxy or ethoxy group,

a piperidin-1-yl or hexahydroazepin-1-yl group which is substituted in the 3 position or in the 4 position by a R_eNR_d group and may additionally be substituted by a C_{1-3} -alkyl group, wherein R_e and R_d are as hereinbefore defined,

a piperidin-1-yl or hexahydroazepin-1-yl- group substituted in the 3 position by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group, wherein in each case two hydrogen atoms at the carbon skeleton of the piperidin-1-yl or hexahydroazepin-1-yl-group are replaced by a straight-chain alkylene bridge, this bridge containing 2 to 5 carbon atoms if the two hydrogen atoms are located on the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are located on adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are located at carbon atoms separated by one atom, or 1 to 3 carbon atoms if the two hydrogen atoms are located at carbon atoms separated by two atoms,

a C_{3-7} -cycloalkyl group substituted by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group,

a C_{3-7} -cycloalkylamino or N-(C_{1-3} -alkyl)- C_{3-7} -cycloalkylamino group substituted in the cycloalkyl moiety by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group wherein the two nitrogen atoms at the cycloalkyl moiety are separated from each other by at least two carbon atoms,

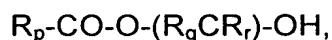
while the phenyl groups mentioned in the definition of the groups mentioned above may independently of one another be mono- or disubstituted by R_h , while the substituents may be identical or different and R_h denotes a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl, C_{1-3} -alkyl or C_{1-3} -alkoxy group,

the isomers and the salts thereof.

The carboxy groups mentioned in the definition of the abovementioned groups may be replaced by a group which can be converted into a carboxy group *in vivo* or by a group which is negatively charged under physiological conditions,

and furthermore the amino and imino groups mentioned in the definition of the abovementioned groups may be substituted by a group which can be cleaved *in vivo*. Such groups are described for example in WO 98/46576 and by N.M. Nielsen *et al.* in International Journal of Pharmaceutics 39, 75-85 (1987).

By a group which can be converted *in vivo* into a carboxy group is meant, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcohol moiety is preferably a C₁₋₆-alkanol, a phenyl-C₁₋₃-alkanol, a C₃₋₉-cycloalkanol, while a C₅₋₈-cycloalkanol may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₅₋₈-cycloalkanol wherein a methylene group in the 3 or 4 position is replaced by an oxygen atom or by an imino group optionally substituted by a C₁₋₃-alkyl, phenyl-C₁₋₃-alkyl, phenyl-C₁₋₃-alkoxycarbonyl or C₂₋₆-alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₄₋₇-cycloalkenol, a C₃₋₅-alkenol, a phenyl-C₃₋₅-alkenol, a C₃₋₅-alkynol or phenyl-C₃₋₅-alkynol with the proviso that no bonds to the oxygen atom start from a carbon atom which carries a double or triple bond, a C₃₋₈-cycloalkyl-C₁₋₃-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C₁₋₃-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula



wherein

R_p denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, phenyl or phenyl-C₁₋₃-alkyl group,

R_q denotes a hydrogen atom, a C₁₋₃-alkyl, C₅₋₇-cycloalkyl or phenyl group and

R_r denotes a hydrogen atom or a C₁₋₃-alkyl group,

by a group which is negatively charged under physiological conditions is meant, for example, a tetrazol-5-yl, phenylcarbonylaminocarbonyl, trifluoromethylcarbonylaminocarbonyl, C₁₋₆-alkylsulphonylamino, phenylsulphonylamino, benzylsulphonylamino, trifluoromethylsulphonylamino, C₁₋₆-alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, benzylsulphonylaminocarbonyl or perfluoro-C₁₋₆-alkylsulphonylaminocarbonyl group

and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as a phenylcarbonyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C₁₋₃-alkyl or C₁₋₃-alkoxy groups, while the substituents may be identical or different, a pyridinoyl group or a C₁₋₁₆-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a C₁₋₁₆-alkoxycarbonyl or C₁₋₁₆-alkylcarbonyloxy group, wherein hydrogen atoms may be wholly or partially replaced by fluorine or chlorine atoms such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxy carbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloroethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, tert.butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy, nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy or hexadecylcarbonyloxy group, a phenyl-C₁₋₆-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a 3-amino-propionyl group wherein the amino group may be mono- or disubstituted by C₁₋₆-alkyl or C₃₋₇-cycloalkyl groups and the substituents may be identical or different, a C₁₋₃-alkylsulphonyl-C₂₋₄-alkoxycarbonyl, C₁₋₃-alkoxy-C₂₋₄-alkoxy-C₂₋₄-alkoxycarbonyl, R_p-CO-O-(R_qCR_r)-O-CO-, C₁₋₆-alkyl-CO-NH-(R_sCR_t)-O-CO- or C₁₋₆-alkyl-CO-O-(R_sCR_t)-(R_sCR_t)-O-CO- group, wherein R_p to R_r are as hereinbefore defined,

R_s and R_t , which may be identical or different, denote hydrogen atoms or C_{1-3} -alkyl groups.

Moreover, the saturated alkyl and alkoxy moieties containing more than 2 carbon atoms mentioned in the definitions above also include the branched isomers thereof such as the isopropyl, tert.butyl, isobutyl group, etc.

R^1 and R^2 may denote, for example a hydrogen atom, a methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 2-propen-1-yl, 2-propyn-1-yl, cyclopropylmethyl, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-(dimethylamino)ethyl, 2-(diethylamino)ethyl, 2-(pyrrolidino)ethyl, 2-(piperidino)ethyl, 2-(morpholino)ethyl, 2-(piperazino)ethyl, 2-(4-methylpiperazino)ethyl, 3-hydroxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3-(dimethylamino)propyl, 3-(diethylamino)propyl, 3-(pyrrolidino)propyl, 3-(piperidino)propyl, 3-(morpholino)propyl, 3-(piperazino)propyl, 3-(4-methylpiperazino)propyl, carboxymethyl, (methoxycarbonyl)methyl, (ethoxycarbonyl)methyl, 2-carboxyethyl, 2-(methoxycarbonyl)ethyl, 2-(ethoxycarbonyl)ethyl, 3-carboxypropyl, 3-(methoxycarbonyl)propyl, 3-(ethoxycarbonyl)propyl, (aminocarbonyl)methyl, (methylaminocarbonyl)methyl, (dimethylamino-carbonyl)methyl, (pyrrolidinocarbonyl)methyl, (piperidinocarbonyl)methyl, (morpholinocarbonyl)methyl, 2-(aminocarbonyl)ethyl, 2-(methylaminocarbonyl)ethyl, 2-(dimethylaminocarbonyl)ethyl, 2-(pyrrolidinocarbonyl)ethyl, 2-(piperidinocarbonyl)ethyl, 2-(morpholinocarbonyl)ethyl, cyanomethyl or 2-cyanoethyl group.

R^3 may denote, for example, a methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, pentyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopropylmethyl, (1-methylcyclopropyl)methyl, (2-methylcyclopropyl)methyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl-, 2-propen-1-yl, 2-methyl-2-propen-1-yl, 3-phenyl-2-propen-1-yl, 2-buten-1-yl, 4,4,4-trifluoro-2-buten-1-yl, 3-buten-1-yl, 2-chloro-2-buten-1-yl, 2-bromo-2-buten-1-yl, 3-

chloro-2-buten-1-yl, 3-bromo-2-buten-1-yl, 2-methyl-2-buten-1-yl, 3-methyl-2-buten-1-yl, 2,3-dimethyl-2-buten-1-yl, 3-trifluoromethyl-2-buten-1-yl, 3-methyl-3-buten-1-yl-, 1-cyclopenten-1-ylmethyl, (2-methyl-1-cyclopenten-1-yl)methyl, 1-cyclohexen-1-ylmethyl, 2-(1-cyclopenten-1-yl)ethyl, 2-propyn-1-yl, 2-butyn-1-yl, 3-butyn-1-yl, benzyl, a fluorobenzyl, chlorobenzyl, bromobenzyl, methylbenzyl, methoxybenzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-furanylmethyl, 3-furanylmethyl, 2-thienylmethyl or 3-thienylmethyl group.

R⁴ may denote, for example, a 3-aminopyrrolidin-1-yl, 3-aminopiperidin-1-yl, 3-(methylamino)-piperidin-1-yl, 3-(ethylamino)-piperidin-1-yl, 3-(dimethylamino)-piperidin-1-yl, 3-(diethylamino)-piperidin-1-yl, 3-[(2-hydroxyethyl)amino]-piperidin-1-yl, 3-[N-methyl-N-(2-hydroxyethyl)-amino]-piperidin-1-yl, 3-[(3-hydroxypropyl)amino]-piperidin-1-yl, 3-[N-methyl-N-(3-hydroxypropyl)-amino]-piperidin-1-yl, 3-[(carboxymethyl)amino]-piperidin-1-yl, 3-[(methoxycarbonylmethyl)amino]-piperidin-1-yl, 3-[(ethoxycarbonylmethyl)amino]-piperidin-1-yl, 3-[N-methyl-N-(methoxycarbonylmethyl)-amino]-piperidin-1-yl, 3-[N-methyl-N-(ethoxycarbonylmethyl)-amino]-piperidin-1-yl, 3-[(2-carboxyethyl)amino]-piperidin-1-yl, 3-{[2-(methoxycarbonyl)ethyl]amino}-piperidin-1-yl, 3-{[2-(ethoxycarbonyl)ethyl]amino}-piperidin-1-yl, 3-{N-methyl-N-[2-(methoxycarbonyl)ethyl]-amino}-piperidin-1-yl, 3-{N-methyl-N-[2-(ethoxycarbonyl)ethyl]-amino}-piperidin-1-yl, 3-[(aminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(methylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(dimethylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(ethylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(diethylaminocarbonylmethyl)amino]-piperidin-1-yl, 3-[(pyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-cyanopyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(4-cyanothiazolidin-3-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-aminocarbonylpyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-[(2-carboxypyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl, 3-{[(2-methoxycarbonylpiperidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl}, 3-{[(2-ethoxycarbonylpiperidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl}, 3-{[(piperidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl}, 3-{[(morpholin-4-ylcarbonylmethyl)amino]-piperidin-1-yl}, 3-amino-2-methyl-piperidin-1-yl, 3-amino-3-methyl-piperidin-1-yl, 3-

amino-4-methyl-piperidin-1-yl, 3-amino-5-methyl-piperidin-1-yl, 3-amino-6-methyl-piperidin-1-yl, 2-amino-8-aza-bicyclo[3.2.1]oct-8-yl, 6-amino-2-aza-bicyclo[2.2.2]oct-2-yl, 4-aminopiperidin-1-yl, 3-amino-hexahydroazepin-1-yl, 4-amino-hexahydroazepin-1-yl, 3-aminocyclopentyl, 3-aminocyclohexyl, 3-(methylamino)-cyclohexyl, 3-(ethylamino)-cyclohexyl, 3-(dimethylamino)-cyclohexyl, 3-(diethylamino)-cyclohexyl, 4-aminocyclohexyl, (2-aminocyclopropyl)amino, (2-aminocyclobutyl)amino, (3-aminocyclobutyl)amino, (2-aminocyclopentyl)amino, (3-aminocyclopentyl)amino, (2-aminocyclohexyl)amino or (3-aminocyclohexyl)amino group.

Preferred compounds of the above general formula I are those wherein

R^1 denotes a hydrogen atom,

a straight-chained or branched C_{1-4} -alkyl group,

a straight-chained or branched C_{1-4} -alkyl group substituted by a group R_a , wherein

R_a denotes a C_{3-6} -cycloalkyl or a phenyl group,

a C_{2-4} -alkyl group terminally substituted by a group R_b , wherein

R_b denotes a hydroxy, C_{1-3} -alkoxy, amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group,

or a C_{3-4} -alkenyl or C_{3-4} .alkynyl group wherein the multiple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R^2 denotes a hydrogen atom or a straight-chained or branched C_{1-3} -alkyl group,

R^3 denotes a straight-chain C_{1-3} -alkyl group terminally substituted by the group R_c , wherein

R_c denotes a C₅₋₆-cycloalkenyl group,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, by a C₁₋₃-alkyl or C₁₋₃-alkoxy group,

a furanyl or thienyl group,

a straight-chain or branched C₃₋₆-alkenyl group wherein the double bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

or a straight-chain or branched C₃₋₆-alkynyl group wherein the triple bond is isolated from the cyclic nitrogen atom by at least one carbon atom and

R⁴ denotes a pyrrolidin-1-yl group which is substituted in the 3 position by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)amino group,

a piperidin-1-yl or hexahydroazepin-1-yl group substituted in the 3 or 4 position by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

a C₅₋₇-cycloalkyl-C₁₋₂-alkyl group which is substituted in the 3 or 4 position by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

a C₅₋₇-cycloalkylamino group which is substituted in the 2 position of the cycloalkyl moiety by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

the isomers and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R¹ denotes a hydrogen atom, a methyl, ethyl, propyl, 2-propyl, butyl, 2-methylpropyl, 2-propen-1-yl, 2-propyn-1-yl, cyclopropylmethyl, benzyl, 2-phenylethyl, 3-

phenylpropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-(dimethylamino)ethyl or 3-(dimethylamino)propyl group,

R² denotes a methyl group,

R³ denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group,

a 1-cyclopenten-1-ylmethyl group,

a 2-butyn-1-yl group,

a benzyl, 2-fluorobenzyl or 3-fluorobenzyl group or

a 2-thienylmethyl group and

R⁴ denotes a 3-aminopyrrolidin-1-yl group,

a 3-aminopiperidin-1-yl or 4-aminopiperidin-1-yl group,

a 3-amino-hexahydroazepin-1-yl or 4-amino-hexahydroazepin-1-yl group,

a 3-aminocyclohexyl group or

a (2-aminocyclohexyl)amino group,

the isomers and salts thereof.

The following preferred compounds are mentioned by way of example:

(1) 1,3-dimethyl-7-benzyl-8-(3-amino-pyrrolidin-1-yl)-xanthine,

(2) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-pyrrolidin-1-yl)-xanthine,

(3) 1,3-dimethyl-7-benzyl-8-(3-amino-piperidin-1-yl)-xanthine,

(4) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(trans-2-amino-cyclohexyl)amino]-xanthine,

(5) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

- (6) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-amino-piperidin-1-yl)-xanthine,
- (7) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(*cis*-2-amino-cyclohexyl)amino]-xanthine,
- (8) 1,3-dimethyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (9) 1,3-dimethyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine,
- (10) 1,3-dimethyl-7-(2-thienylmethyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (11) 1,3-dimethyl-7-(3-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (12) 1,3-dimethyl-7-(2-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (13) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (14) 1,3-dimethyl-7-(2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (15) 1,3-bis-(cyclopropylmethyl)-7-benzyl-8-(3-amino-piperidin-1-yl)-xanthine,
- (16) (*R*)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (17) (*S*)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (18) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-hexahydroazepin-1-yl)-xanthine,
- (19) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-amino-hexahydroazepin-1-yl)-xanthine,

(20) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(cis-3-amino-cyclohexyl)-xanthine-hydrochloride and

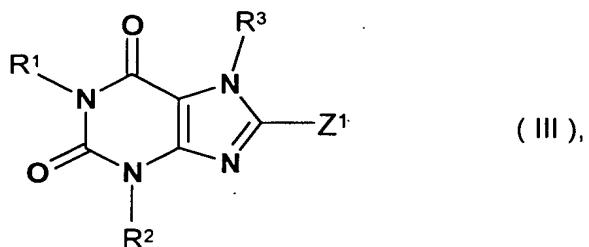
(21) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-methylamino-piperidin-1-yl)-xanthine

and the salts thereof.

According to the invention, the compounds of general formula I are obtained by methods known *per se*, for example by the following methods:

a) In order to prepare compounds of general formula I wherein R⁴ is one of the abovementioned groups linked to the xanthine skeleton via a nitrogen atom:

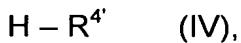
reacting a compound of general formula



wherein

R¹ to R³ are as hereinbefore defined and

Z¹ denotes a leaving group such as a halogen atom, a substituted hydroxy or sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group, with a compound of general formula



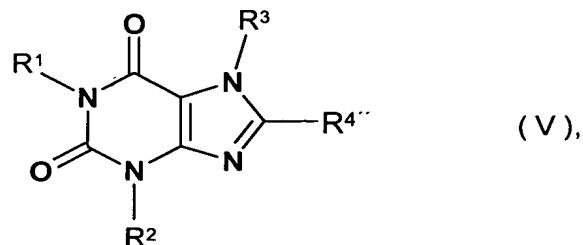
wherein

R^{4'} denotes one of the groups mentioned for R⁴ hereinbefore, which is linked to the xanthine skeleton of general formula I via a nitrogen atom.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxan, toluene, chlorobenzene, dimethylformamide, dimethylsulphoxide, methylene chloride, ethylene glycol monomethylether, ethylene glycol diethylether or sulpholane optionally in the presence of an inorganic or tertiary organic base, e.g. sodium carbonate or potassium hydroxide, a tertiary organic base, e.g. triethylamine, or in the presence of N-ethyl-diisopropylamine (Hünig base), while these organic bases may simultaneously serve as solvent, and optionally in the presence of a reaction accelerator such as an alkali metal halide or a palladium-based catalyst at temperatures between -20 and 180°C, preferably however at temperatures between -10 and 120°C. The reaction may however also be carried out without a solvent or in an excess of the compound of general formula IV used.

b) In order to prepare a compound of general formula I wherein R⁴ according to the definition given earlier contains an amino group or an alkylamino group optionally substituted in the alkyl moiety:

deprotecting a compound of general formula



wherein R¹, R² and R³ are as hereinbefore defined and R^{4'} contains an N-tert.-butyloxycarbonylamino group or an N-tert.-butyloxycarbonyl-N-alkylamino group, wherein the alkyl moiety of the N-tert.-butyloxycarbonyl-N-alkylamino group may be substituted as mentioned hereinbefore.

The tert.-butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with bromotrimethylsilane or

iodotrimethylsilane, optionally using a solvent such as methylene chloride, ethyl acetate, dioxan, methanol or diethyl ether at temperatures between 0 and 80°C.

If according to the invention a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I or

if a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I or

if a compound of general formula I is obtained which contains a carboxy group, this may be converted by esterification into a corresponding ester of general formula I or

if a compound of general formula I is obtained which contains a carboxy or ester group, this may be converted by reaction with an amine into a corresponding amide of general formula I.

The subsequent esterification is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan or particularly advantageously in a corresponding alcohol optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent ester formation may also be carried out by reacting a compound which contains a carboxy group with a corresponding alkyl halide.

The subsequent acylation or sulphonylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan with a corresponding acyl or sulphonyl derivative optionally in the presence of a tertiary organic base or in the presence of an inorganic base or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethylsulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde, acetone or butyraldehyde in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride conveniently at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, e.g. with hydrogen in the presence of

palladium/charcoal, at a hydrogen pressure of 1 to 5 bar. The methylation may also be carried out in the presence of formic acid as reducing agent at elevated temperature, e.g. at temperatures between 60 and 120°C.

The subsequent amide formation is carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding amine optionally in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan, while the amine used may simultaneously serve as solvent, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or with a corresponding carboxylic acid in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert-butyl, trityl, benzyl or tetrahydropyranyl group,

protecting groups for a carboxy group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, benzyl,

methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxan/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at ambient temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably from 3 to 5 bar. However, a 2,4-dimethoxybenzyl group is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.-butyl or tert.-butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxan, methanol or diethyl ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxan at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known per se (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active

alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

The compounds of general formulae III and IV used as starting materials are either known from the literature or may be obtained by methods known from the literature (cf. Examples I to VIII).

For example, a starting compound of general formula III may be obtained by reacting a theophylline derivative halogenated in the 8 position with a correspondingly substituted alkyl halide.

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme DPP-IV.

The biological properties of the new compounds were investigated as follows:

The ability of the substances and their corresponding salts to inhibit the DPP-IV activity can be demonstrated in an experiment in which an extract of the human colon carcinoma cell line Caco-2 is used as the DPP IV source. This cell line was obtained from the American Type Culture Collection (ATCC HTB 37). The differentiation of the cells in order to induce the DPP-IV expression was carried out in accordance with the description by Reiher et al. in an article entitled "Increased expression of intestinal cell line Caco-2" , which appeared in Proc. Natl. Acad. Sci. Vol. 90, pp. 5757-5761 (1993). The cell extract was obtained from cells solubilised in a buffer (10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% Nonidet-P40, pH 8.0) by centrifugation at 35,000 g for 30 minutes at 4°C (to remove cell debris).

The DPP-IV assay was carried out as follows:

50 µl of substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, were placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1 % DMSO) was pipetted in. The reaction was started by the addition of 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances under investigation were typically added prediluted to 20 µl, while the volume of assay buffer was then reduced accordingly. The reaction was carried out at ambient temperature, the incubation period was 60 minutes. Then the fluorescence was measured in a Victor 1420 Multilabel Counter, with the excitation wavelength at 405 nm and the emission wavelength at 535 nm. Dummy values (corresponding to 0 % activity) were obtained in mixtures with no Caco-2 protein (volume replaced by assay buffer), control values (corresponding to 100 % activity) were obtained in mixtures without any added substance. The potency of the test substances in question, expressed as IC₅₀ values, were calculated from dosage/activity curves consisting of 11 measured points in each case. The following results were obtained:

Compound (Example No.)	DPP IV inhibition IC50 [nM]
1 (2)	82
1(6)	230
2(1)	22

The compounds prepared according to the invention are well tolerated as no toxic side effects could be detected in rats after the oral administration of 30 mg/kg of the compound of Example 1(2), for example.

In view of their ability to inhibit DPP-IV activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for influencing any conditions or diseases which can be affected by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or conditions such as type I and type II diabetes mellitus, arthritis, obesity, allograft transplantation and osteoporosis caused by calcitonin. Additionally, on the basis of the role of the glucagon-like peptides such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is expected that the compounds according to the invention will be suitable for achieving, *inter alia*, a sedative or tranquillising effect, as well as having a favourable effect on catabolic states after operations or hormonal stress responses or possibly reducing mortality and morbidity after myocardial infarct. Moreover, they are suitable for treating any conditions connected with the effects mentioned above and mediated by GLP-1 or GLP-2. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for preventing and treating acute kidney failure. It is also expected that DPP-IV inhibitors and hence the compounds according to the invention can be used to treat infertility or to improve fertility in humans or mammals, if the infertility is connected with insulin resistance and particularly with polycystic ovary syndrome.

The compounds according to the invention may also be used in conjunction with other active substances. Suitable therapeutic agents for such combinations include for example antidiabetic agents such metformin, sulphonylureas (e.g. glibenclamid, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinediones (e.g. rosiglitazone, pioglitazone), PPAR-gamma-agonists (e.g. GI 262570), alpha-glucosidase inhibitors (e.g. acarbose, voglibose), insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin) or amylin, lipid lowering agents such as for example HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin) or fibrates (e.g. bezafibrat, fenofibrat) or active substances for treating obesity, such as sibutramin or tetrahydrolipstatin.

The dosage required to achieve such an effect is appropriately 1 to 100 mg, preferably 1 to 30 mg, by intravenous route, and 1 to 1000 mg, preferably 1 to 100 mg, by oral route, in each case administered 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples which follow are intended to illustrate the invention

Preparation of the starting compounds:

Example I

1,3-dimethyl-7-benzyl-8-chloro-xanthine

A mixture of 20 g of 8-chlorotheophylline, 150 ml of dimethylformamide, 10.2 ml of benzyl bromide and 15.5 ml of N-ethyl-diisopropylamine is stirred overnight at ambient temperature. The reaction mixture is poured onto 600 ml of water. The solid is suction filtered, washed with water and diethylether and dried.

Yield: 14.6 g (51 % of theory)

Melting point: 155°C

R_f value: 0.84 (silica gel, ethyl acetate/methanol = 9:1)

The following compounds are obtained analogously to Example I:

(1) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-chloro-xanthine

Melting point: 104 °C

R_f value: 0.55 (silica gel, methylene chloride/methanol = 20:1)

(2) 1,3-dimethyl-7-(2-butyn-1-yl)-8-chloro-xanthine

Melting point: 105-108 °C

R_f value: 0.55 (silica gel, methylene chloride/methanol = 20:1)

(3) 1,3-dimethyl-7-[(1-cyclopenten-1-yl)methyl]-8-chloro-xanthine

R_f value: 0.50 (silica gel, methylene chloride/methanol = 20:1)

(4) 1,3-dimethyl-7-(2-thienylmethyl)-8-chloro-xanthine

R_f value: 0.35 (silica gel, methylene chloride/methanol = 50:1)

Mass spectrum (EI): m/z = 310, 312 [M]⁺

(5) 1,3-dimethyl-7-(3-fluorobenzyl)-8-chloro-xanthine

R_f value: 0.60 (silica gel, methylene chloride/methanol = 20:1)

(6) 1,3-dimethyl-7-(2-fluorobenzyl)-8-chloro-xanthine

Mass spectrum (EI): m/z = 322, 324 [M]⁺

(7) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(cis-3-tert.-butyloxycarbonylamino-cyclohexyl)-xanthine

(8) 1,3-dimethyl-7-(4-fluorobenzyl)-8-chloro-xanthine

R_f value: 0.60 (silica gel, methylene chloride/methanol = 20:1)

(9) 1,3-dimethyl-7-(2-buten-1-yl)-8-chloro-xanthine

R_f value: 0.70 (silica gel, methylene chloride/methanol = 10:1)

Example II

(R)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 1 g of 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-chloro-xanthine, 1.32 g of (R)-3-tert.-butyloxycarbonylamino-piperidine, 1 ml of triethylamine and 10 ml of dimethylformamide is stirred at 50°C for two and a half days. The reaction mixture is diluted with 100 ml of water and then extracted with ethyl acetate. The organic phase is dried, evaporated down and the residue is stirred with diethylether. The solid is suction filtered and dried.

Yield: 1.0 g (63 % of theory)

Melting point: 164°C

R_f value: 0.36 (aluminium oxide, cyclohexane/ethyl acetate = 1:1)

The following compounds are obtained analogously to Example II:

(1) (S)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Melting point: 164°C

Mass spectrum (ESI⁺): m/z = 445 [M-H]⁺

(2) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonylamino)-hexahydroazepin-1-yl]-xanthine

Melting point: 154°C

Mass spectrum (ESI⁻): m/z = 459 [M-H]⁻

(3) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[4-(tert.-butyloxycarbonylamino)-hexahydroazepin-1-yl]-xanthine

Mass spectrum (ESI⁻): m/z = 459 [M-H]⁻

R_f value: 0.67 (silica gel, éthyl acetate)

Example III

3-(tert.-butyloxycarbonylamino)-hexahydroazepine

2 g of 1-benzyl-3-(tert.-butyloxycarbonylamino)-hexahydroazepine in 20 ml of methanol are hydrogenated for 24 hours at ambient temperature under a hydrogen pressure of 3 bar in the presence of 200 mg palladium on activated charcoal (10% Pd). Then the catalyst is removed by suction filtering and the filtrate is evaporated to dryness.

Yield: 1.3 g (90 % of theory)

Melting point: 78°C

Mass spectrum (ESI⁺): m/z = 215 [M+H]⁺

The following compounds are obtained analogously to Example III:

(1) (S)-3-(tert.-butyloxycarbonylamino)-piperidine

Melting point: 122°C

Mass spectrum (ESI⁺): m/z = 201 [M+H]⁺

(2) (R)-3-(tert.-butyloxycarbonylamino)-piperidine

The starting material, (R)-1-benzyl-3-(tert.-butyloxycarbonylamino)-piperidine, was prepared analogously to the (S)-enantiomer known from the literature (Moon, Sung-Hwan; Lee, Sujin; Synth.Commun.; 28; 21; 1998; 3919-3926)

Melting point: 119°C

Mass spectrum (ESI⁺): m/z = 201 [M+H]⁺

(3) 4-(tert.-butyloxycarbonylamino)-hexahydroazepine

Mass spectrum (ESI⁺): m/z = 215 [M+H]⁺

R_f value: 0.02 (aluminium oxide, cyclohexane/ethyl acetate = 1:1)

Example IV

1-benzyl-3-(tert.-butyloxycarbonylamino)-hexahydroazepine

Prepared by reacting 1-benzyl-3-amino-hexahydrobenzazepine with di-tert.butyl pyrocarbonate

Melting point: 48-50°C

Mass spectrum (ESI⁺): m/z = 305 [M+H]⁺

The following compounds are obtained analogously to Example IV:

(1) 1-benzyl-4-(tert.-butyloxycarbonylamino)-hexahydroazepine

Mass spectrum (ESI⁺): m/z = 305 [M+H]⁺

R_f value: 0.79 (aluminium oxide, cyclohexane/ethyl acetate = 1:1)

Example V

1,3-dimethyl-8-(cis-3-tert.-butyloxycarbonylamino-cyclohexyl)-xanthine

Prepared from the compound of Example VI by treating with 4N sodium hydroxide solution in methanol at 100°C in a bomb tube

Example VI

1,3-dimethyl-5-[(cis-3-tert.-butyloxycarbonylamino-cyclohexyl)-carbonylamino]-6-amino-uracil

Prepared from 5,6-diamino-1,3-dimethyluracil and cis-3-tert.-butyloxycarbonylamino-cyclohexanecarboxylic acid in the presence of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and N-ethyl-diisopropylamine in dimethylformamide at ambient temperature

Example VII

1,3-bis-(cyclopropylmethyl)-7-benzyl-8-chloro-xanthine

Prepared from the compound of Example VIII by refluxing with N-chlorosuccinimide in 1,2-dichloroethane.

Mass spectrum (ESI⁺): m/z = 407, 409 [M+Na]⁺

Example VIII

1,3-bis-(cyclopropylmethyl)-7-benzyl-xanthine

Prepared from 7-benzyl-xanthine by reacting with cyclopropylmethylbromide in dimethylformamide in the presence of caesium carbonate

Mass spectrum (ESI⁺): m/z = 351 [M+H]⁺

Preparation of the final compounds:

Example 1

1,3-dimethyl-7-benzyl-8-(3-amino-pyrrolidin-1-yl)-xanthine

A mixture of 200 mg of 1,3-dimethyl-7-benzyl-8-chloro-xanthine, 420 mg of 3-amino-pyrrolidine-dihydrochloride, 0.92 ml of triethylamine and 2 ml of dimethylformamide is stirred for 2 days at 50°C. The reaction mixture is diluted with 20 ml of water and extracted twice with 10 ml of ethyl acetate. The organic phase is washed with saturated saline solution, dried and evaporated down. The residue is crystallised with diethylether/diisopropylether (1:1). The solid is suction filtered and dried.

Yield: 92 mg (40 % of theory)

Melting point: 150 °C

Mass spectrum (ESI⁺): m/z = 355 [M+H]⁺

R_f value: 0.08 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

The following compounds are obtained analogously to Example 1:

(1) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-pyrrolidin-1-yl)-xanthine

Melting point: 119 °C

Mass spectrum (ESI⁺): m/z = 333 [M+H]⁺

R_f value: 0.07 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

(2) 1,3-dimethyl-7-benzyl-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI $^+$): m/z = 369 [M+H] $^+$

R_f value: 0.06 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

(3) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(trans-2-amino-cyclohexyl)amino]-xanthine

Mass spectrum (ESI $^+$): m/z = 361 [M+H] $^+$

(4) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI $^+$): m/z = 347 [M+H] $^+$

(5) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI $^+$): m/z = 347 [M+H] $^+$

(6) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(cis-2-amino-cyclohexyl)amino]-xanthine

Mass spectrum (ESI $^+$): m/z = 361 [M+H] $^+$

(7) 1,3-dimethyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI $^+$): m/z = 331 [M+H] $^+$

R_f value: 0.08 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

(8) 1,3-dimethyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI $^+$): m/z = 359 [M+H] $^+$

R_f value: 0.09 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

(9) 1,3-dimethyl-7-(2-thienylmethyl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI $^+$): m/z = 375 [M+H] $^+$

R_f value: 0.08 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

(10) 1,3-dimethyl-7-(3-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 387 [M+H]⁺

R_f value: 0.08 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

(11) 1,3-dimethyl-7-(2-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 387 [M+H]⁺

R_f value: 0.08 (silica gel, ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0,1)

(12) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 387 [M+H]⁺

(13) 1,3-dimethyl-7-(2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 333 [M+H]⁺

(14) 1,3-bis-(cyclopropylmethyl)-7-benzyl-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 449 [M+H]⁺

Example 2

(R)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

980 mg of (R)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine in 12 ml methylene chloride are combined with 3 ml of trifluoroacetic acid and stirred for 2 hours at ambient temperature. Then the mixture is diluted with methylene chloride and made alkaline with 1 M sodium hydroxide solution. The organic phase is separated off, dried and evaporated to dryness.

Yield: 680 mg (89 % of theory)

Mass spectrum (ESI⁺): m/z = 347 [M+H]⁺

R_f value: 0.20 (aluminium oxide, ethyl acetate/methanol = 9:1)

The following compounds are obtained analogously to Example 2:

(1) (S)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 347 [M+H]⁺

(2) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-hexahydroazepin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 361 [M+H]⁺

(3) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-amino-hexahydroazepin-1-yl)-xanthine

Mass spectrum (ESI⁺): m/z = 361 [M+H]⁺

(4) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(cis-3-amino-cyclohexyl)-xanthine-hydrochloride

The reaction was carried out with hydrochloric acid.

¹H-NMR (400 MHz, 6 mg in 0.5 ml DMSO-d₆, 30°C): characteristic signals at 3.03 ppm (1H, m, H-1) and 3.15 ppm (1H, m, H-3)

Example 3

1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-methylamino-piperidin-1-yl)-xanthine

154 mg of 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine and 0.032 ml of aqueous formaldehyde solution (37 % by weight) in 0.5 ml of methanol are combined with 24 mg of sodium borohydride and stirred at ambient temperature.

0.01 ml of formaldehyde solution and 10 mg of sodium borohydride are both added twice more and stirring is continued at ambient temperature. The reaction mixture is combined with 1M sodium hydroxide solution and repeatedly extracted with ethyl acetate. The organic phases are combined, dried and evaporated down. The residue is purified by chromatography over an aluminium oxide column with ethyl acetate/methanol.

Yield: 160 mg (25% of theory)

Mass spectrum (ESI⁺): m/z = 361 [M+H]⁺

R_f value: 0.80 (aluminium oxide, ethyl acetate/methanol = 4:1)

The following compounds may also be obtained analogously to the foregoing Examples and other methods known from the literature:

- (1) 7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (2) 1-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (3) 3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (4) 1-ethyl-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (5) 1-propyl-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (6) 1-(2-propyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (7) 1-butyl-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (8) 1-(2-butyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (9) 1-(2-methylpropyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (10) 1-(2-propen-1-yl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (11) 1-(2-propyn-1-yl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (12) 1-cyclopropylmethyl-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(13) 1-benzyl-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(14) 1-(2-phenylethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(15) 1-(2-hydroxyethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(16) 1-(2-methoxyethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(17) 1-(2-ethoxyethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(18) 1-[(2-(dimethylamino)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(19) 1-[(2-(diethylamino)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(20) 1-[(2-(pyrrolidin-1-yl)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(21) 1-[(2-(piperidin-1-yl)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(22) 1-[(2-(morpholin-4-yl)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(23) 1-[(2-(piperazin-1-yl)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(24) 1-[(2-(4-methyl-piperazin-1-yl)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(25) 1-(3-hydroxypropyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(26) 1-(3-methoxypropyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(27) 1-(3-ethoxypropyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(28) 1-[(3-(dimethylamino)propyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(29) 1-[(3-(diethylamino)propyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(30) 1-[(3-(pyrrolidin-1-yl)propyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(31) 1-[(3-(piperidin-1-yl)propyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(32) 1-[(3-(morpholin-4-yl)propyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(33) 1-[(3-(piperazin-1-yl)propyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(34) 1-[(3-(4-methyl-piperazin-1-yl)propyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(35) 1-(carboxymethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(36) 1-(methoxycarbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(37) 1-(ethoxycarbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(38) 1-(2-carboxyethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(39) 1-[(2-(methoxycarbonyl)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(40) 1-[(2-(ethoxycarbonyl)ethyl]-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(41) 1-(aminocarbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(42) 1-(methylaminocarbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(43) 1-(dimethylaminocarbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(44) 1-(pyrrolidin-1-yl-carbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

- (45) 1-(piperidin-1-yl-carbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (46) 1-(morpholin-4-yl-carbonylmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (47) 1-(cyanmethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (48) 1-(2-cyanethyl)-3-methyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (49) 1-methyl-3-ethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (50) 1-methyl-3-propyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (51) 1-methyl-3-(2-propyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (52) 1-methyl-3-butyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (53) 1-methyl-3-(2-butyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (54) 1-methyl-3-(2-methylpropyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (55) 1-methyl-3-(2-propen-1-yl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine
- (56) 1-methyl-3-(2-propyn-1-yl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(57) 1-methyl-3-cyclopropylmethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(58) 1-methyl-3-benzyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(59) 1-methyl-3-(2-phenylethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(60) 1-methyl-3-(2-hydroxyethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(61) 1-methyl-3-(2-methoxyethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(62) 1-methyl-3-(2-ethoxyethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(63) 1-methyl-3-[(2-(dimethylamino)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(64) 1-methyl-3-[(2-(diethylamino)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(65) 1-methyl-3-[(2-(pyrrolidin-1-yl)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(66) 1-methyl-3-[(2-(piperidin-1-yl)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(67) 1-methyl-3-[(2-(morpholin-4-yl)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(68) 1-methyl-3-[(2-(piperazin-1-yl)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(69) 1-methyl-3-[(2-(4-methyl-piperazin-1-yl)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(70) 1-methyl-3-(3-hydroxypropyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(71) 1-methyl-3-(3-methoxypropyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(72) 1-methyl-3-(3-ethoxypropyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(73) 1-methyl-3-[(3-(dimethylamino)propyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(74) 1-methyl-3-[(3-(diethylamino)propyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(75) 1-methyl-3-[(3-(pyrrolidin-1-yl)propyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(76) 1-methyl-3-[(3-(piperidin-1-yl)propyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(77) 1-methyl-3-[(3-(morpholin-4-yl)propyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(78) 1-methyl-3-[(3-(piperazin-1-yl)propyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(79) 1-methyl-3-[(3-(4-methyl-piperazin-1-yl)propyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(80) 1-methyl-3-(carboxymethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(81) 1-methyl-3-(methoxycarbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(82) 1-methyl-3-(ethoxycarbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(83) 1-methyl-3-(2-carboxyethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(84) 1-methyl-3-[(2-(methoxycarbonyl)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(85) 1-methyl-3-[(2-(ethoxycarbonyl)ethyl]-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(86) 1-methyl-3-(aminocarbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(87) 1-methyl-3-(methylaminocarbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(88) 1-methyl-3-(dimethylaminocarbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(89) 1-methyl-3-(pyrrolidin-1-yl-carbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(90) 1-methyl-3-(piperidin-1-yl-carbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(91) 1-methyl-3-(morpholin-4-yl-carbonylmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(92) 1-methyl-3-(cyanmethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(93) 1-methyl-3-(2-cyanethyl)-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(94) 1,3,7-trimethyl-8-(3-amino-piperidin-1-yl)-xanthine

(95) 1,3-dimethyl-7-ethyl-8-(3-amino-piperidin-1-yl)-xanthine

(96) 1,3-dimethyl-7-propyl-8-(3-amino-piperidin-1-yl)-xanthine

(97) 1,3-dimethyl-7-(2-propyl)-8-(3-amino-piperidin-1-yl)-xanthine

(98) 1,3-dimethyl-7-butyl-8-(3-amino-piperidin-1-yl)-xanthine

(99) 1,3-dimethyl-7-(2-butyl)-8-(3-amino-piperidin-1-yl)-xanthine

(100) 1,3-dimethyl-7-(2-methylpropyl)-8-(3-amino-piperidin-1-yl)-xanthine

(101) 1,3-dimethyl-7-pentyl-8-(3-amino-piperidin-1-yl)-xanthine

(102) 1,3-dimethyl-7-(2-methylbutyl)-8-(3-amino-piperidin-1-yl)-xanthine

(103) 1,3-dimethyl-7-(3-methylbutyl)-8-(3-amino-piperidin-1-yl)-xanthine

(104) 1,3-dimethyl-7-(2,2-dimethylpropyl)-8-(3-amino-piperidin-1-yl)-xanthine

(105) 1,3-dimethyl-7-cyclopropylmethyl-8-(3-amino-piperidin-1-yl)-xanthine

(106) 1,3-dimethyl-7-[(1-methylcyclopropyl)methyl]-methylbutyl)-8-(3-amino-piperidin-1-yl)-xanthine

(107) 1,3-dimethyl-7-[(2-methylcyclopropyl)methyl]-methylbutyl)-8-(3-amino-piperidin-1-yl)-xanthine

(108) 1,3-dimethyl-7-cyclobutylmethyl-8-(3-amino-piperidin-1-yl)-xanthine

(109) 1,3-dimethyl-7-cyclopentylmethyl-8-(3-amino-piperidin-1-yl)-xanthine

(110) 1,3-dimethyl-7-cyclohexylmethyl-8-(3-amino-piperidin-1-yl)-xanthine

(111) 1,3-dimethyl-7-[2-(cyclopropyl)ethyl]- methylbutyl)-8-(3-amino-piperidin-1-yl)-xanthine

(112) 1,3-dimethyl-7-(2-propen-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(113) 1,3-dimethyl-7-(2-methyl-2-propen-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(114) 1,3-dimethyl-7-(3-phenyl-2-propen-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(115) 1,3-dimethyl-7-(2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(116) 1,3-dimethyl-7-(4,4,4-trifluor-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(117) 1,3-dimethyl-7-(3-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(118) 1,3-dimethyl-7-(2-chloro-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(119) 1,3-dimethyl-7-(2-bromo-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(120) 1,3-dimethyl-7-(3-chloro-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(121) 1,3-dimethyl-7-(3-bromo-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(122) 1,3-dimethyl-7-(2-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(123) 1,3-dimethyl-7-(2,3-dimethyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(124) 1,3-dimethyl-7-(3-trifluoromethyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(125) 1,3-dimethyl-7-(3-methyl-3-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(126) 1,3-dimethyl-7-[(2-methyl-1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine

(127) 1,3-dimethyl-7-(1-cyclohexen-1-yl-methyl)-8-(3-amino-piperidin-1-yl)-xanthine

(128) 1,3-dimethyl-7-[2-(1-cyclopenten-1-yl)ethyl]-8-(3-amino-piperidin-1-yl)-xanthine

(129) 1,3-dimethyl-7-(2-propyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(130) 1,3-dimethyl-7-(3-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine

(131) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(132) 1,3-dimethyl-7-(2-chlorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(133) 1,3-dimethyl-7-(3-chlorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(134) 1,3-dimethyl-7-(4-chlorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(135) 1,3-dimethyl-7-(2-bromobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(136) 1,3-dimethyl-7-(3-bromobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(137) 1,3-dimethyl-7-(4-bromobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(138) 1,3-dimethyl-7-(2-methylbenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(139) 1,3-dimethyl-7-(3-methylbenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(140) 1,3-dimethyl-7-(4-methylbenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(141) 1,3-dimethyl-7-(2-methoxybenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(142) 1,3-dimethyl-7-(3-methoxybenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(143) 1,3-dimethyl-7-(4-methoxybenzyl)-8-(3-amino-piperidin-1-yl)-xanthine

(144) 1,3-dimethyl-7-(2-phenylethyl)-8-(3-amino-piperidin-1-yl)-xanthine

(145) 1,3-dimethyl-7-(3-phenylpropyl)-8-(3-amino-piperidin-1-yl)-xanthine

(146) 1,3-dimethyl-7-(2-furanylmethyl)-8-(3-amino-piperidin-1-yl)-xanthine

(146) 1,3-dimethyl-7-(3-furanylmethyl)-8-(3-amino-piperidin-1-yl)-xanthine

- (147) 1,3-dimethyl-7-(2-thienylmethyl)-8-(3-amino-piperidin-1-yl)-xanthine
- (148) 1,3-dimethyl-7-(3-thienylmethyl)-8-(3-amino-piperidin-1-yl)-xanthine
- (149) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-methylamino-piperidin-1-yl)-xanthine
- (150) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-ethylamino-piperidin-1-yl)-xanthine
- (151) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-dimethylamino-piperidin-1-yl)-xanthine
- (152) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-diethylamino-piperidin-1-yl)-xanthine
- (153) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(2-hydroxyethyl)amino]-piperidin-1-yl}-xanthine
- (154) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[N-methyl-N-(2-hydroxyethyl)-amino]-piperidin-1-yl}-xanthine
- (155) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(3-hydroxypropyl)amino]-piperidin-1-yl}-xanthine
- (156) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[N-methyl-N-(3-hydroxypropyl)-amino]-piperidin-1-yl}-xanthine
- (157) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(carboxymethyl)amino]-piperidin-1-yl}-xanthine

(158) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(methoxycarbonylmethyl)amino]-piperidin-1-yl}-xanthine

(159) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(ethoxycarbonylmethyl)amino]-piperidin-1-yl}-xanthine

(160) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[N-methyl-N-(methoxycarbonylmethyl)-amino]-piperidin-1-yl}-xanthine

(161) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[N-methyl-N-(ethoxycarbonylmethyl)-amino]-piperidin-1-yl}-xanthine

(162) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(2-carboxyethyl)amino]-piperidin-1-yl}-xanthine

(163) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-[[2-(methoxycarbonyl)ethyl]amino]-piperidin-1-yl)-xanthine

(164) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-[[2-(ethoxycarbonyl)ethyl]amino]-piperidin-1-yl)-xanthine

(165) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-{N-methyl-N-[2-(methoxycarbonyl)ethyl]-amino}-piperidin-1-yl)-xanthine

(166) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-{N-methyl-N-[2-(ethoxycarbonyl)ethyl]-amino}-piperidin-1-yl)-xanthine

(167) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(aminocarbonylmethyl)amino]-piperidin-1-yl}-xanthine

(168) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(methylaminocarbonylmethyl)-amino]-piperidin-1-yl}-xanthine

- (169) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(dimethylaminocarbonylmethyl)-amino]-piperidin-1-yl}-xanthine
- (170) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(ethylaminocarbonylmethyl)-amino]-piperidin-1-yl}-xanthine
- (171) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(diethylaminocarbonylmethyl)-amino]-piperidin-1-yl}-xanthine
- (172) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(pyrrolidin-1-ylcarbonylmethyl)-amino]-piperidin-1-yl}-xanthine
- (173) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(2-cyanopyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl}-xanthine
- (174) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(4-cyanothiazolidin-3-ylcarbonylmethyl)amino]-piperidin-1-yl}-xanthine
- (175) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(2-aminocarbonylpyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl}-xanthine
- (176) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(2-carboxypyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl}-xanthine
- (177) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(2-methoxycarbonylpyrrolidin-1-ylcarbonylmethyl)amino]-piperidin-1-yl}-xanthine
- (178) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(piperidin-1-ylcarbonylmethyl)-amino]-piperidin-1-yl}-xanthine

(179) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-{3-[(morpholin-4-ylcarbonylmethyl)-amino]-piperidin-1-yl}-xanthine

(180) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(2-methyl-3-amino-piperidin-1-yl)-xanthine

(181) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-methyl-3-amino-piperidin-1-yl)-xanthine

(182) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-methyl-3-amino-piperidin-1-yl)-xanthine

(183) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(5-methyl-3-amino-piperidin-1-yl)-xanthine

(184) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(6-methyl-3-amino-piperidin-1-yl)-xanthine

(185) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(2-amino-8-aza-bicyclo[3.2.1]oct-8-yl)-xanthine

(186) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(6-amino-2-aza-bicyclo[2.2.2]oct-2-yl)-xanthine

(187) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-cyclopentyl)-xanthine

(188) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-methylamino-cyclohexyl)-xanthine

(189) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-ethylamino-cyclohexyl)-xanthine

(190) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-dimethylamino-cyclohexyl)-xanthine

(191) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-diethylamino-cyclohexyl)-xanthine

(192) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-amino-cyclohexyl)-xanthine

(193) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(3-amino-cyclohexyl)amino]-xanthine

(194) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(2-amino-cyclopentyl)amino]-xanthine

(195) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(3-amino-cyclopentyl)amino]-xanthine

(196) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(2-amino-cyclobutyl)amino]-xanthine

(197) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(3-amino-cyclobutyl)amino]-xanthine

(198) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(2-amino-cyclopropyl)amino]-xanthine

Example 4

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	<u>1.5 mg</u>
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 5

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
maize starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	<u>2.0 mg</u>
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, 'biplanar, faceted on both sides and notched on one side.

Example 6

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
maize starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	<u>1.0 mg</u>
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 7

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance	150.0 mg
dried maize starch	approx. 180.0 mg
powdered lactose.	approx. 87.0 mg
magnesium stearate	<u>3.0 mg</u>
	approx. 420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 8

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitanmonostearate	<u>840.0 mg</u>
	2000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 9

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance	1.00 g
Na salt of carboxymethylcellulose	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g
flavouring	0.30 g
dist. water	ad 100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 10

Ampoules containing 10 mg of active substance

Composition:

active substance	10.0 mg
0,01 N hydrochloric acid	q.s.
twice-distilled water	ad 2.0 ml

Preparation:

The active substance is dissolved in the requisite amount of 0.01 N HCl, made isotonic with saline, sterile filtered and transferred into 2 ml ampoules.

Example 11

Ampoules containing 50 mg of active substance

Composition:

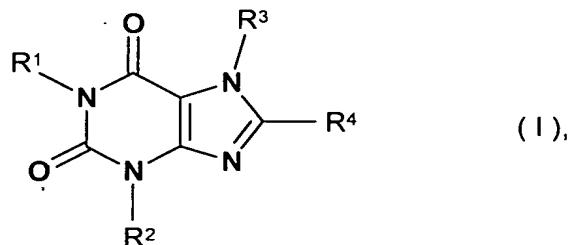
active substance	50.0 mg
0.01 N hydrochloric acid	q.s.
twice-distilled water	ad 10.0 ml

Preparation:

The active substance is dissolved in the requisite amount of 0.01 N HCl, made isotonic with saline, sterile filtered and transferred into 10 ml ampoules.

Patent Claims

1. Compounds of general formula



R¹ denotes a hydrogen atom,

a straight-chained or branched C₁₋₆-alkyl group,

a straight-chained or branched C₁₋₆-alkyl group substituted by a group R_a, wherein

R_a denotes a C₃₋₇-cycloalkyl, phenyl, cyano, carboxy, C₁₋₃-alkoxy-carbonyl, aminocarbonyl, C₁₋₃-alkylamino-carbonyl, di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

a straight-chained or branched C₂₋₆-alkyl group substituted by a group R_b, wherein

R_b is isolated by at least two carbon atoms from the cyclic nitrogen atom and

R_b denotes a hydroxy, C₁₋₃-alkoxy, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl or 4-ethylpiperazin-1-yl group,

a C₃₋₆-cycloalkyl group,

or a C₃₋₄-alkenyl or C₃₋₄-alkynyl group wherein the multiple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R² denotes a hydrogen atom,

a straight-chained or branched C₁₋₆-alkyl group,

a straight-chained or branched C₁₋₆-alkyl group substituted by a group R_a, wherein

R_a denotes a C₃₋₇-cycloalkyl, phenyl, cyano, carboxy, C₁₋₃-alkoxy-carbonyl, aminocarbonyl, C₁₋₃-alkylamino-carbonyl or di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

a straight-chained or branched C₂₋₆-alkyl group substituted by an R_b group, wherein

R_b is isolated from the cyclic nitrogen atom by at least two carbon atoms and

R_b denotes a hydroxy, C₁₋₃-alkoxy, amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl or 4-ethylpiperazin-1-yl group,

a C₃₋₆-cycloalkyl group,

or a C₃₋₄-alkenyl or C₃₋₄-alkynyl group, wherein the multiple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R³ denotes a straight-chained or branched C₁₋₆-alkyl group,

a straight-chained or branched C₁₋₆-alkyl group substituted by a group R_c wherein

R_c denotes a C₃₋₇-cycloalkyl group optionally substituted by a C₁₋₃-alkyl group,

a C₅₋₇-cycloalkenyl group optionally substituted by a C₁₋₃-alkyl group,

a phenyl group optionally substituted as defined hereinafter or

a furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group optionally substituted by one or two methyl or ethyl groups,

a straight-chain or branched C₃₋₈-alkenyl group, wherein the double bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

a straight-chain or branched C₃₋₆-alkenyl group substituted by a chlorine or bromine atom or a phenyl or trifluoromethyl group, wherein the double bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

or a straight-chain or branched C₃₋₆-alkynyl group wherein the triple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R⁴ denotes an azetidin-1-yl or pyrrolidin-1-yl group which is substituted in the 3 position by a R_eNR_d group and may additionally be substituted by a C₁₋₃-alkyl group, wherein

R_e denotes a hydrogen atom or a C₁₋₃-alkyl group and

R_d denotes a hydrogen atom, a C₁₋₃-alkyl group, an R_f-C₁₋₃-alkyl group or an R_g-C₂₋₃-alkyl group, wherein

R_f denotes a carboxy, C₁₋₃-alkyloxy-carbonyl, aminocarbonyl, C₁₋₃-alkyl-amino-carbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, 2-cyanopyrrolidin-1-yl-carbonyl, 2-carboxypyrrolidin-1-yl-carbonyl,

2-methoxycarbonylpyrrolidin-1-yl-carbonyl, 2-ethoxycarbonylpyrrolidin-1-yl-carbonyl, 2-aminocarbonylpyrrolidin-1-yl-carbonyl, 4-cyanothiazolidin-3-yl-carbonyl, 4-carboxythiazolidin-3-yl-carbonyl, 4-methoxycarbonylthiazolidin-3-yl-carbonyl, 4-ethoxy-carbonylthiazolidin-3-yl-carbonyl, 4-aminocarbonylthiazolidin-3-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-methyl-piperazin-1-yl-carbonyl or 4-ethyl-piperazin-1-yl-carbonyl group and

R_g , which is separated by two carbon atoms from the nitrogen atom of the R_eNR_d group, denotes a hydroxy, methoxy or ethoxy group,

a piperidin-1-yl or hexahydroazepin-1-yl group which is substituted in the 3 position or in the 4 position by a R_eNR_d group and may additionally be substituted by a C_{1-3} -alkyl group, wherein R_e and R_d are as hereinbefore defined,

a piperidin-1-yl or hexahydroazepin-1-yl- group substituted in the 3 position by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group, wherein in each case two hydrogen atoms at the carbon skeleton of the piperidin-1-yl or hexahydroazepin-1-yl-group are replaced by a straight-chain alkylene bridge, this bridge containing 2 to 5 carbon atoms if the two hydrogen atoms are located on the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are located on adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are located at carbon atoms separated by one atom, or 1 to 3 carbon atoms if the two hydrogen atoms are located at carbon atoms separated by two atoms,

a C_{3-7} -cycloalkyl group substituted by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group,

a C_{3-7} -cycloalkylamino or N-(C_{1-3} -alkyl)- C_{3-7} -cycloalkylamino group substituted in the cycloalkyl moiety by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group wherein

the two nitrogen atoms at the cycloalkyl moiety are separated from each other by at least two carbon atoms,

while the phenyl groups mentioned in the definition of the groups mentioned above may independently of one another be mono- or disubstituted by R_h , while the substituents may be identical or different and R_h denotes a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl, C₁₋₃-alkyl or C₁₋₃-alkoxy group,

the isomers and the salts thereof.

2. Compounds of general formula I according to claim 1, wherein

R^1 denotes a hydrogen atom,

a straight-chained or branched C₁₋₄-alkyl group,

a straight-chained or branched C₁₋₄-alkyl group substituted by a group R_a , wherein

R_a denotes a C₃₋₆-cycloalkyl or a phenyl group,

a C₂₋₄-alkyl group terminally substituted by a group R_b , wherein

R_b denotes a hydroxy, C₁₋₃-alkoxy, amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

or a C₃₋₄-alkenyl or C₃₋₄-alkynyl group wherein the multiple bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

R^2 denotes a hydrogen atom or a straight-chained or branched C₁₋₃-alkyl group,

R^3 denotes a straight-chain C₁₋₃-alkyl group terminally substituted by the group R_c , wherein

R_c denotes a C_{5-6} -cycloalkenyl group,

a phenyl group optionally substituted by a fluorine, chlorine or bromine atom, by a C_{1-3} -alkyl or C_{1-3} -alkoxy group,

a furanyl or thienyl group,

a straight-chain or branched C_{3-6} -alkenyl group wherein the double bond is isolated from the cyclic nitrogen atom by at least one carbon atom,

or a straight-chain or branched C_{3-6} -alkynyl group wherein the triple bond is isolated from the cyclic nitrogen atom by at least one carbon atom and

R^4 denotes a pyrrolidin-1-yl group which is substituted in the 3 position by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)amino group,

a piperidin-1-yl or hexahydroazepin-1-yl group substituted in the 3 or 4 position by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group,

a C_{5-7} -cycloalkyl- C_{1-2} -alkyl group which is substituted in the 3 or 4 position by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group,

a C_{5-7} -cycloalkylamino group which is substituted in the 2 position of the cycloalkyl moiety by an amino, C_{1-3} -alkylamino or di-(C_{1-3} -alkyl)-amino group,

the isomers and the salts thereof.

3. Compounds of general formula I according to claim 1, wherein

R^1 denotes a hydrogen atom, a methyl, ethyl, propyl, 2-propyl, butyl, 2-methylpropyl, 2-propen-1-yl, 2-propyn-1-yl, cyclopropylmethyl, benzyl, 2-phenylethyl, 3-

phenylpropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-(dimethylamino)ethyl or 3-(dimethylamino)propyl group,

R² denotes a methyl group,

R³ denotes a 2-buten-1-yl or 3-methyl-2-buten-1-yl group,

a 1-cyclopenten-1-ylmethyl group,

a 2-butyn-1-yl group,

a benzyl, 2-fluorobenzyl or 3-fluorobenzyl group or

a 2-thienylmethyl group and

R⁴ denotes a 3-aminopyrrolidin-1-yl group,

a 3-aminopiperidin-1-yl or 4-aminopiperidin-1-yl group,

a 3-amino-hexahydroazepin-1-yl or 4-amino-hexahydroazepin-1-yl group,

a 3-aminocyclohexyl group or

a (2-aminocyclohexyl)amino group,

the isomers and salts thereof.

4. The following compounds of general formula I according to claim 1:

(1) 1,3-dimethyl-7-benzyl-8-(3-amino-pyrrolidin-1-yl)-xanthine,

(2) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-pyrrolidin-1-yl)-xanthine,

(3) 1,3-dimethyl-7-benzyl-8-(3-amino-piperidin-1-yl)-xanthine,

(4) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(trans-2-amino-cyclohexyl)amino]-xanthine,

(5) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,

- (6) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-amino-piperidin-1-yl)-xanthine,
- (7) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-[(*cis*-2-amino-cyclohexyl)amino]-xanthine,
- (8) 1,3-dimethyl-7-(2-butyn-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (9) 1,3-dimethyl-7-[(1-cyclopenten-1-yl)methyl]-8-(3-amino-piperidin-1-yl)-xanthine,
- (10) 1,3-dimethyl-7-(2-thienylmethyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (11) 1,3-dimethyl-7-(3-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (12) 1,3-dimethyl-7-(2-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (13) 1,3-dimethyl-7-(4-fluorobenzyl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (14) 1,3-dimethyl-7-(2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (15) 1,3-bis-(cyclopropylmethyl)-7-benzyl-8-(3-amino-piperidin-1-yl)-xanthine,
- (16) (*R*)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (17) (*S*)-1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-piperidin-1-yl)-xanthine,
- (18) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-amino-hexahydroazepin-1-yl)-xanthine,
- (19) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(4-amino-hexahydroazepin-1-yl)-xanthine,

(20) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(cis-3-amino-cyclohexyl)-xanthine-hydrochloride and

(21) 1,3-dimethyl-7-(3-methyl-2-buten-1-yl)-8-(3-methylamino-piperidin-1-yl)-xanthine

and the salts thereof.

5. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 4 with inorganic or organic acids or bases.

6. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 4 or a physiologically acceptable salt according to claim 5 optionally together with one or more inert carriers and/or diluents.

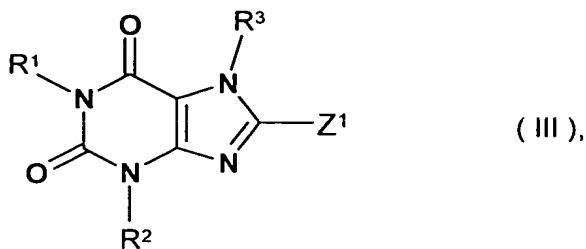
7. Use of a compound according to at least one of claims 1 to 5 for preparing a pharmaceutical composition which is suitable for treating type I and type II diabetes mellitus, arthritis, obesity, allograft transplantation and osteoporosis caused by calcitonin.

8. Process for preparing a pharmaceutical composition according to claim 6, characterised in that a compound according to at least one of claims 1 to 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

9. Process for preparing the compounds of general formula I according to claims 1 to 5, characterised in that

a) In order to prepare compounds of general formula I wherein R⁴ is one of the groups mentioned in claim 1 linked to the xanthine skeleton via a nitrogen atom:

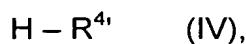
a compound of general formula



wherein

R¹ to R³ are defined as in claims 1 to 4 and

Z¹ denotes a leaving group such as a halogen atom, a substituted hydroxy or sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group, is reacted with a compound of general formula

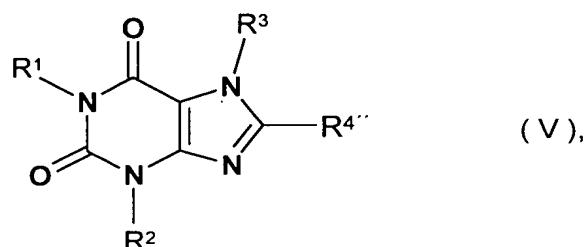


wherein

R⁴ⁱ denotes one of the groups defined for R⁴ in claims 1 to 4 which is linked to the xanthine skeleton of general formula I via a nitrogen atom,

b) In order to prepare compounds of general formula I wherein R⁴ according to the definition hereinbefore contains an amino group or an alkylamino group optionally substituted in the alkyl moiety:

a compound of general formula



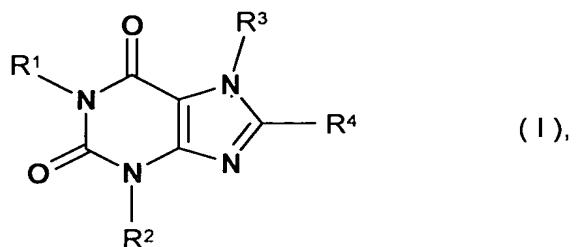
wherein R¹, R² and R³ are defined as in claims 1 to 4 and

R^{4''} contains an N-tert.-butyloxycarbonylamino group or an N-tert.-butyloxycarbonyl-N-alkylamino group, wherein the alkyl moiety of the N-tert.-butyloxycarbonyl-N-alkyl-amino group may be substituted as in claims 1 to 4,

is deprotected.

Abstract

The present invention relates to substituted xanthines of general formula



wherein R¹ to R⁴ are defined as in claim 1, the tautomers and the stereoisomers thereof, mixtures thereof, the prodrugs and the salts thereof which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV).